

Attorney Docket No.: PENN-0701  
Inventors: Alain H. Rook  
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pharmaceutically acceptable carrier and an adjunct therapeutic agent which stimulates interferon- $\gamma$  production.

#### REMARKS

Claims 1, 3 and 4 are pending in this application. Claims 1, 3 and 4 have been rejected. Claims 1, 3 and 4 have been amended. No new matter has been added by these amendments to the claims. Reconsideration is respectfully requested in light of these amendments and the following remarks.

#### **I. Rejection of Claims Under 35 U.S.C. § 102(b)**

The rejection of claim 1 under 35 U.S.C. § 102(b) as being anticipated by Rook et al. (Clin. Exp. Immunol. 1997 January, 107 Suppl 1: 16-20) has been maintained for reasons of record. The Examiner further suggests that the declaration filed under 37 CFR 1.131 is ineffective to overcome the rejection as this declaration is insufficient to establish a reduction to practice of the invention prior to the effective date of the prior art reference. In addition, the Examiner continues to suggest that the reference at least clearly suggests the clinical application of IL-12 to treat human CTCL and provides a reasonable

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expectation of success because such a clinical trial must have been approved by the FDA.

Applicants respectfully point out that the Examiner has overstated the importance of a Phase I clinical trial being started in terms of FDA approval. Phase I clinical trials are merely safety studies wherein escalating doses of a candidate compound are given to humans, usually to healthy volunteers, sometimes to patients with a disease. A Phase I clinical study is not a study of the efficacy of a drug, or the ability of a candidate compound to produce a pharmacological effect that has therapeutic potential. Therefore, a mere statement in a paper that a Phase I clinical study is underway is not evidence that FDA has "approved" that drug for any purpose other than use of the drug in a dose-escalating safety study. FDA approval doesn't come until a drug has been demonstrated to be both safe and effective in Phase III clinical studies. Clearly, a statement in a paper that a Phase I study is underway is not enabling for one of skill to understand that the drug being tested in a Phase I trial will have efficacy to treat disease. In fact, the doses administered in a Phase I study are not designed to prove efficacy, only safety. As a result, this reference does not anticipate the instant invention whose claims are drawn to

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treatment based on actual *in vivo* data showing pharmacological activity and therapeutic efficacy in humans. With respect to the Examiner's comment that the declaration fails to provide evidence of a reduction to practice before the effective date of the reference, the Applicants respectfully point out that the reduction to practice is provided by the specification as filed, not by a mere statement in this prior art reference. Accordingly, withdrawal of this rejection is respectfully requested.

## **II. Rejection of Claims Under 35 U.S.C. § 103(a)**

The rejection of claims 1 and 3 under 35 U.S.C. § 103(a) as being unpatentable over Rook et al. (Ann. NY Acad, 1996, 795:310-318) in view of Verbik et al. (Clin. Exp. Metastasis, 1996, 14:219-229) has been maintained for reasons of record. The Examiner suggests that the Applicants arguments put forth in the previous reply were not persuasive. In particular, the Examiner suggests that the requirement for a reasonable expectation of success does not rest on a complete certainty of success and that virtually all clinical applications are based on *in vitro* and/or *in vivo* animal studies. The Examiner has also suggested that

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Applicants have misquoted the Verbik reference. Applicants respectfully disagree with the Examiner's conclusions.

To establish a *prima facie* case of obviousness under 35 U.S.C. 103(a) three basic criteria must be met. MPEP § 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all of the claim limitations.

The cited combination of prior art references fails to meet all of these criteria with respect to the instant claimed invention.

The Examiner has rejected claims 1 and 3, suggesting that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to design a method of treatment of advanced CTCL in a human by administering IL-12 based upon the teachings of Rook et al. (Referencing IL-12 deficiency and normalization of IFN- $\gamma$  by exogenous IL-12 in SzS PBMCs). The Examiner suggests that one skilled in the art would be motivated to do so as Verbik et al. teach strongly toward an expectation of success *in vivo*.

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At the outset, and contrary to the Examiner's suggestion, Applicants have not misquoted the reference of Verbik et al. As stated in the earlier reply, "Verbik et al. teach administration of IL-12 to mice suffering from liver lymphoma. Even as such, the use of IL-12 with other interleukins caused unexplained early deaths in test mice. As is taught on page 227 of the reference, the IL-12 is believed to have induced secretion of IFN- $\gamma$  causing gastrointestinal damage to the tissue of the mice resulting in their death. Further, mice undergoing radiation after administration of IL-12 suffered severe gastrointestinal damage which was much more pronounced than damage induced by radiation alone, page 227, column 2. Verbik et al. further teach that the mechanisms through which the IL-12 mediates *in vivo* anti-tumor responses is not fully understood." Therefore, Applicants clearly understood that the early deaths were in a group receiving combined treatment. However, the point made was that it was the IL-12 that the authors believed was leading to toxicity. Therefore, this reference clearly puts into question the safe use of IL-12 as far as choosing doses for administration to humans. In addition, although the Examiner is correct in stating that most cancer chemotherapy agents have negative effects, the presence of such negative effects are often a

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deciding factor when one of skill decides whether or not to test an agent. The fact that Verbik et al. teach that early deaths results, not just a minor negative effect, indicates that the use of IL-12 in conjunction with other therapies especially needs to be shown to be safe before testing in humans is begun. In fact, it is the Phase I clinical study that shows such safety, a study that had not been performed before the filing of the instant specification, as stated in the declaration filed with the previous response.

In the case of the reference of Rook et al. cited by the Examiner, as acknowledged by the Examiner, Rook et al. (1996) teach *in vitro* culture experiments with PBMCs and the single cytokine IL-12 but do not teach a method for *in vivo* treatment. Therefore, neither of the references cited under 35 U.S.C. 103(a) teach or suggest that *in vivo* treatment with IL-12 in conjunction with an adjunct therapeutic agent would be expected to produce a therapeutically effective response in humans. It must be remembered as well that one of the criteria for establishing a *prima facie* case of obviousness is that in order to be combined there must be some suggestion or motivation in the references themselves. Such motivation is also lacking in the cited references as the reference of Verbik et al. focuses only on use

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of IL-12 while Rook et al. fails to teach that IL-12 should be combined with any adjunct agents as well.

Accordingly, neither of the cited prior art references provide one of skill in the art with a reasonable expectation of successfully treating advanced cutaneous T cell lymphoma in a human via administration of IL-12 alone or in combination with an adjunct therapeutic agent, as claimed in instant claims 1 and 3. In addition, there is no suggestion or teaching in the cited references to combine reference teachings. Thus, one skilled in the art would not be motivated to administer IL-12 to a human with any expectation of success. On the contrary, a skilled person would refrain from administering interleukin-12, alone or in combination with other interleukins to a human based upon the teachings of Rook et al. (1996) and Verbik et al. However, in an earnest effort to advance the prosecution, Applicants have amended claim 3 to specify a specific dose range of IL-12 to be administered to humans for treatment of advanced CTCL, a limitation that is not taught or suggested specifically in the prior art references cited by the Examiner. Support for this amendment can be found throughout the specification as filed but in particular at page 8, lines 4-9. Withdrawal of this rejection is, therefore, respectfully requested.

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The Examiner has also maintained the rejection of claim 3 as being unpatentable over Rook et al. and Verbik et al., as applied to claims 1-3, and further in view of Rook et al. (Clin. Exp. Immunol., 1997, 107 Suppl. 1:16-20) for the reasons cited in the earlier Office Action. In this case, the Examiner again suggests that the Applicants arguments presented in the previous reply were not persuasive. Specifically, the Examiner suggests that Rook clearly teaches that *in vitro* studies led to a phase I trial of IL-12 to treat CTCL, which is administration to a human and that as such indicates FDA approval of IL-12 therapy in humans. The Examiner also suggests that such FDA approval was gained based on Rook's *in vitro* results and would suggest a reasonable expectation of success in human application, absent evidence to the contrary. Applicants respectfully disagree with the Examiner's conclusions.

As discussed *supra*, Rook et al.(1996) teach *in vitro* culture experiments with PBMCs and the single cytokine IL-12. Rook et al.(1996) do not teach a composition comprising recombinant IL-12 with IL-18 or IFN- $\alpha$ .

As discussed *supra*, Verbik teaches away from treatment by a composition of both IL-12 and adjunct therapeutic agents which

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stimulate the production of INF- $\gamma$ , see page 227. As it is suggested to have caused death in some test mice. Further, it teaches that lethally irradiated mice treated with IL-12 had severe gastrointestinal damage which was much more pronounced than damage that was induced by radiation alone, page 227.

Rook et al. (1997) teach that the PMBCs of CTCL patients exhibit an increased production of T-helper type 2 cytokines (IL-4 and IL-5) and deficient Th1 cytokines (IL-2 and IFN- $\alpha$ ). Rook et al. (1997) teach *in vitro* culture experiments with IL-12 and suggests that IL-12 and IFN- $\alpha$  may suppress the growth of CD4T cells *in vitro*.

Therefore, as discussed in detail *supra*, Verbik et al. teach that administration of IL-12 is believed to induce secretion of IL- $\gamma$  causing gastrointestinal damage to test mice, resulting in early death. Thus, there would be no motivation to administer **both** IL-12 and IL- $\gamma$  or IL-12 and retinoids (which increase IL- $\gamma$  production) to a human. This is because one of skill would expect that in doing so the toxicity pattern of the combined treatment would lead to a greater toxicity response, especially in humans where the therapy had not yet been shown to be safe. Additionally, as discussed in the specification as

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filed, the cytokine pathways exhibit complex regulatory responses and as a result, there would not be a reasonable expectation of success of the administration of IL-12 in combination with IL- $\gamma$  or a retinoid. Therefore, the fact that IL-12 had been shown to be pharmacologically active *in vitro*, combined with the fact that in mice IL-12 also had pharmacological activity but in the presence of significant toxicity (early death), would not have led one of skill in the art to combine reference teachings and expect success in treating humans.

MPEP § 2143 and the Courts are quite clear; both the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The cited combination of prior art fails to provide this reasonable expectation of success. It is only with the instant specification in hand, which demonstrates the efficacy of Applicant's invention that one of skill has a reasonable expectation of success. Accordingly, this combination of prior art fails to establish a *prima facie* case of obviousness as set forth in MPEP 2143. However, in an earnest effort to advance the prosecution, Applicants have amended claim 3 to specify a specific dose range of IL-12 to be

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administered to humans for treatment of advanced CTCL, a limitation that is not taught or suggested specifically in the prior art references cited by the Examiner. Support for this amendment can be found throughout the specification as filed but in particular at page 8, lines 4-9. Withdrawal of this rejection is respectfully requested.

Finally, claims 4 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Rook et al. (1996). The Examiner suggests that although this reference does not teach a method of *in vivo* treatment that it would have been *prima facie* obvious for one of ordinary skill to design a method for treatment of CTCL in humans based on the strong teaching of Rook et al. and suggestions that SzS, an advanced form of CTCL, is characterized by marked depression of IFN- $\gamma$  production and a defect in IL-12 production by PBMCs. Further, the Examiner suggests that one of skill would have been motivated to treat CTCL by administering IL-12 with an adjunct agent that stimulates IFN- $\gamma$  production at Rook's suggestion and would have reasonably expected success because such combination would correct both defects of IL-12 and IFN- $\gamma$  in these patients. Then, the Examiner acknowledges that this reference is silent about a pharmaceutically acceptable

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carrier but that this is well known in the art. Applicants's respectfully disagree with the Examiner's conclusions.

Claim 4 is drawn to a method of treatment of advanced CTCL in humans comprising administering an effective amount of recombinant IL-12 in a pharmaceutically acceptable carrier and an adjunct agent that stimulates IFN- $\gamma$  production. As discussed *supra*, Rook et al.(1996) teach *in vitro* culture experiments with PBMCs and the single cytokine IL-12. Rook et al.(1996) do not teach a composition comprising recombinant IL-12 with an adjunct therapeutic agent that stimulates production of IFN- $\gamma$ , as is disclosed and claimed in the instant invention. Further, as discussed *supra*, MPEP § 2143 and the Courts are quite clear; both the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The cited combination of prior art fails to provide this reasonable expectation of success. It is only with the instant specification in hand, which demonstrates the efficacy of Applicant's invention that one of skill has a reasonable expectation of success. Accordingly,

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this combination of prior art fails to establish a *prima facie* case of obviousness as set forth in MPEP 2143.

However in an earnest effort to advance the prosecution of this case, Applicants have amended claim 4 to refer to specific dose ranges of IL-12 for treatment of humans, dose ranges that are not taught or suggested by the prior art reference. Accordingly, withdrawal of this rejection is respectfully requested.

### **III. Conclusion**

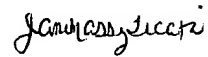
Applicant believes that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment, captioned "Version with

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Markings to Show Changes Made". Also attached is a Declaration  
by the inventor.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

The claims have been amended as follows:

1. (amended) A method for treatment of advanced cutaneous T cell lymphoma in a human comprising administering to a human ~~an effective amount~~ 100 to 300 ng/ml of recombinant interleukin-12 in a pharmaceutically acceptable carrier.

3. (amended) A composition for treatment of advanced cutaneous T cell lymphoma in a human comprising a solution of 100 to 300 ng/ml of recombinant interleukin-12 and an adjunct therapeutic agent which stimulates interferon- $\gamma$  production, said adjunct therapeutic agent comprising a retinoid, interleukin 18, interferon- $\alpha$  or interferon- $\gamma$ .

4. (amended) A method for treatment of advanced cutaneous T cell lymphoma in a human comprising administering to a human ~~an effective amount~~ 100 to 300 ng/ml of recombinant interleukin-12 in a pharmaceutically acceptable carrier and an adjunct therapeutic agent which stimulates interferon- $\gamma$  production.